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(54) Title: ONCOLYTIC COMBINATIONS FOR THE TREATMENT OF CANCER

(57) Abstract: Leukotriene (LTB_4) antagonists enhance the effectiveness of 2',2'-difluoronucleoside anti-cancer agents.

ONCOLYTIC COMBINATIONS FOR THE TREATMENT OF CANCER

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority from United States Provisional Patent Application No. 60/164,716 filed 11 November 1999, the entire disclosure of which is incorporated herein by reference.

FIELD OF THE INVENTION

This invention relates to a method of treating cancer with anti-cancer agents. More specifically, it relates to the use of 2',2'-difluoronucleosides anti-cancer agents, in conjunction with leukotriene (LTB_4) antagonists which enhance the effectiveness of the anti-cancer agent.

BACKGROUND OF THE INVENTION

Leukotriene B_4 (LTB_4) is a proinflammatory lipid which has been implicated in the pathogenesis of psoriasis, arthritis, chronic lung diseases, acute respiratory distress syndrome, shock, asthma, inflammatory bone diseases and other inflammatory states characterized by the infiltration and activation of polymorphonuclear leukocytes and other pro inflammatory cells. Thus activated, the polymorphonuclear leukocytes liberate tissue-degrading enzymes and reactive chemicals causing the inflammation. US Patent 5,462,954 discloses phenylphenol leukotriene antagonists which are useful in the treatment of psoriasis, arthritis, chronic lung diseases, acute respiratory distress syndrome, shock,

asthma, inflammatory bone diseases and other inflammatory states characterized by the infiltration and activation of polymorphonuclear leukocytes and other proinflammatory cells. US Patent 5,910,505 discloses that certain phenylphenol leukotriene B_4 (LTB_4) antagonists are useful as agents for the treatment of oral squamous cell carcenoma. US Patent 5,543,428 discloses a group of phenylphenol leukotriene antagonists which have the property of reversing multi drug resistance in tumor cells. The use of the leukotriene inhibitor will reverse the drug resistance of resistance of resistant tumor cells to vinblasine, vincristine, vindesine navebine, daunorubicin, doxorubicin mitroxantrone, etoposide, teniposide, mitomycine, actinomycin, taxol, topotecan, mithramycin, colchicine, puromycin, podophylotoxin, emetine, gramicidin, and valinomycin

BRIEF SUMMARY OF THE INVENTION

This invention provides compositions and methods useful for treating cancers which are not multi-drug resistant. The compositions of the present invention include the 2',2'-difluoronucleoside anti-cancer agents described in US Patent 5,464,826 (the disclosure of which is incorporated herein by reference) in combination with leukotriene (LTB_4) antagonists of formula I and formula II.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is a horizontal bar graph displaying the data from Table 1 provided in the "ASSAY EXAMPLE 1", infra. The vertical axis of the graph is the figure forms the origin of the numbered horizontal bars, wherein

each bar is a separate Treatment as set out in the Tables. The horizontal axis is tumor growth delay (TGD) in days.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions:

The term, "Active Ingredient" refers to leukotriene B4 antagonist compounds generically described by formula A as well as diphenyl leukotriene B_4 antagonist compounds generically described by formula I and formula II or the list of specific diphenyl compounds disclosed, infra., and the salts, solvates, and prodrugs of such compounds.

The term, "LTB_4 antagonist" means any agent that inhibits the actions of LTB_4 of its synthesis, or increases its biochemical breakdown.

The terms, "mammal" and "mammalian" include human.

The term "therapeutically effective interval" is a period of time beginning when one of either (a) the 2', 2'-difluoronuceoside anti-cancer agent or (b) the LTB_4 antagonist is administered to a mammal and ending at the limit of the anti-cancer beneficial effect in treating cancer of (a) or (b). Typically, the anti-cancer agents and the leukotriene (LTB_4) antagonist are administered within 24 hours of each other, more preferably within 4 hours and most preferably within 1 hour.

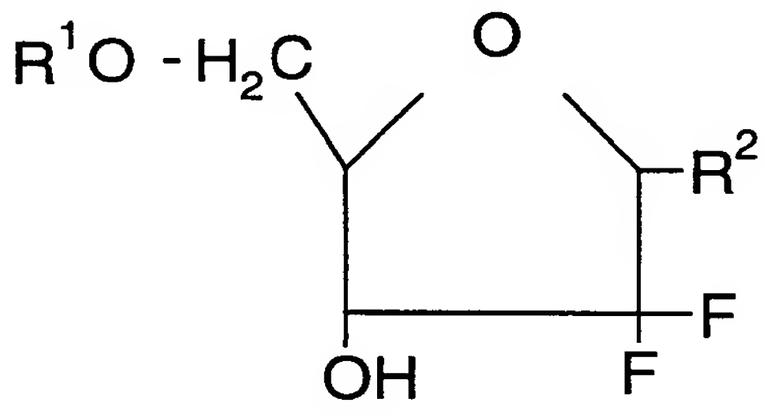
The phrase "therapeutically effective combination", used in the practice of this invention, means administration of both (a) the anti-cancer agent, and (b)

the LTB_4 antagonist, either simultaneously or separately, in any order.

Suprisingly, we have found that the combination of 2',2'-difluoro nucleoside anti-cancer agents with leukotriene antagonists (LTB_4) antagonists act synergistically against cancers which are not multi-drug resistant.

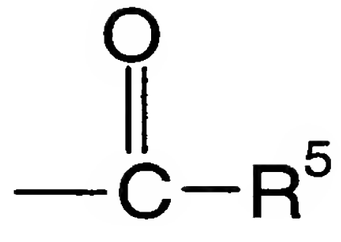
The types of cancers which may be treated with the compositions of the present invention include anti cancer agents: Breast Carcinoma, Bladder Carcinoma, Colorectal Carcinoma, Esophageal Carcinoma, Gastric Carcinoma, Germ Cell Carcinoma e.g. Testicular Cancer, Gynecologic Carcinoma, Lymphoma - Hodgkin's, Lymphoma - Non-Hodgkin's, Malignant Melanoma, Multiple Myeloma, Neurologic Carcinoma, Brain Cancer, Non-Small Cell Lung Cancer, Pancreatic Carcinoma, Prostate Carcinoma, Ewings Sarcoma, Osteosarcoma, Small Cell Lung Tumor, Soft Tissue Sarcoma, Pediatric Malignancies and the like.

The anti cancer agents which may be used are compounds of the formula:

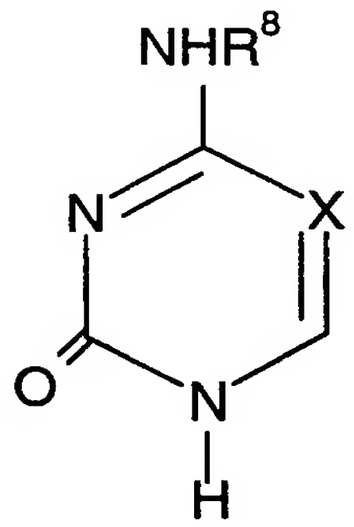


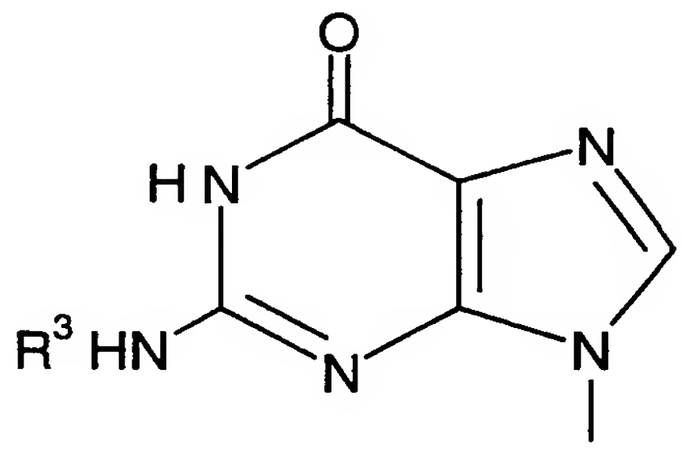
wherein:

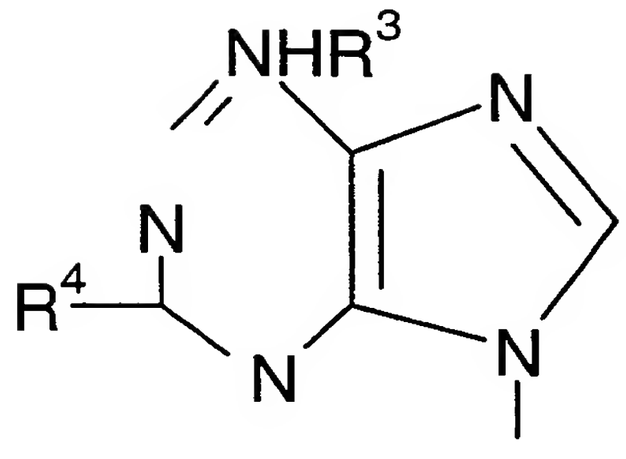
R^2 is hydrogen or



R^2 is a base defined by one of the formulae

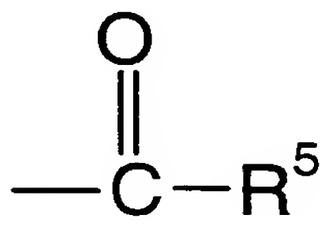






X is N or C-R^4

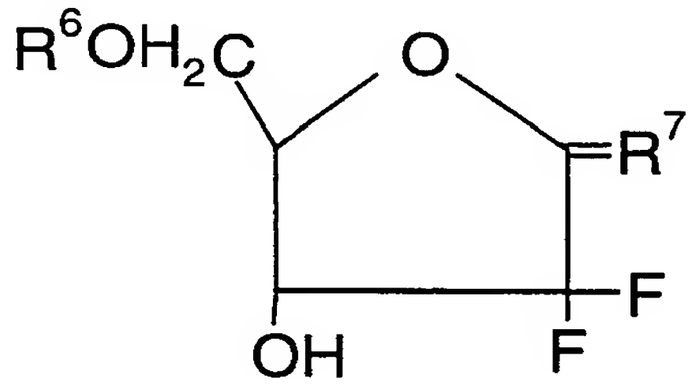
R^3 is hydrogen, C_1-C_4 alkyl or



R^4 is hydrogen, C_1-C_4 alkyl, amino, bromo, fluoro, chloro or iodo;

Each R^5 independently is hydrogen or C_1-C_4 alkyl; and the pharmaceutically-acceptable salts thereof.

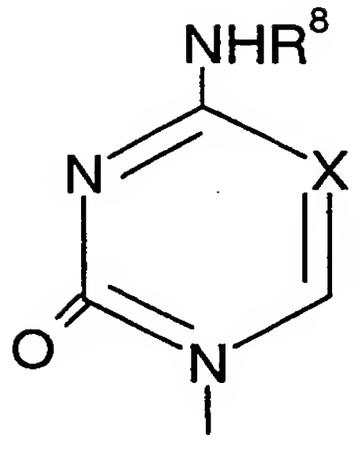
The following compounds may also be used

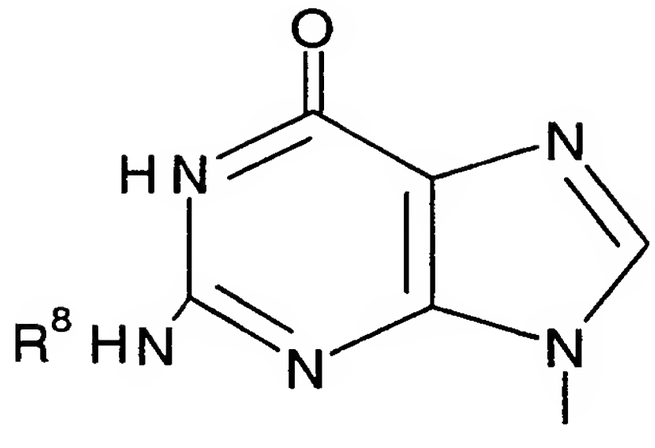


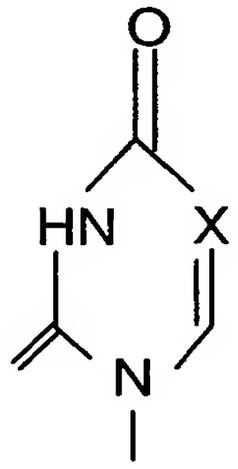
wherein:

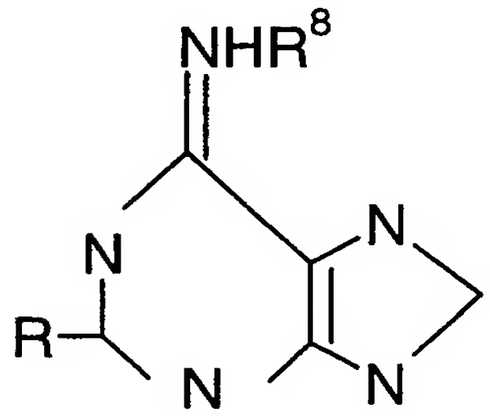
R^6 is hydrogen, C_1-C_4 alkyl;

R^7 is a base of one of the formulae







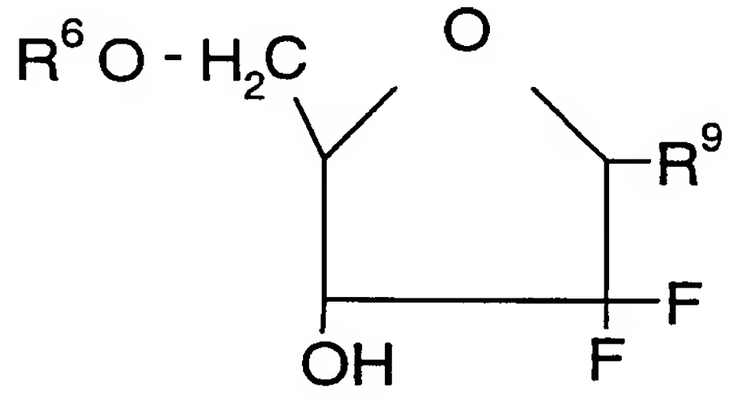


wherein:

X is N or C-R^4;

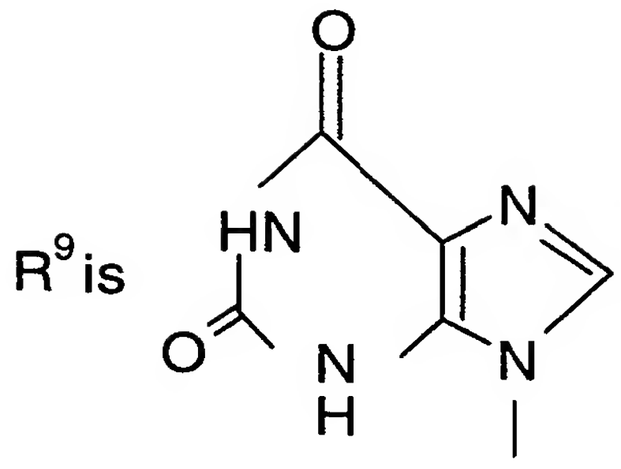
R^8 is hydrogen or C_1-C_4 alkyl;

R^4 is hydrogen, C_1-C_4 alkyl; amino, bromo, fluoro, chloro and iodo; and the pharmaceutically-acceptable salts thereof; with the proviso that R^6 and R^8 may both be hydrogen only when X is N and



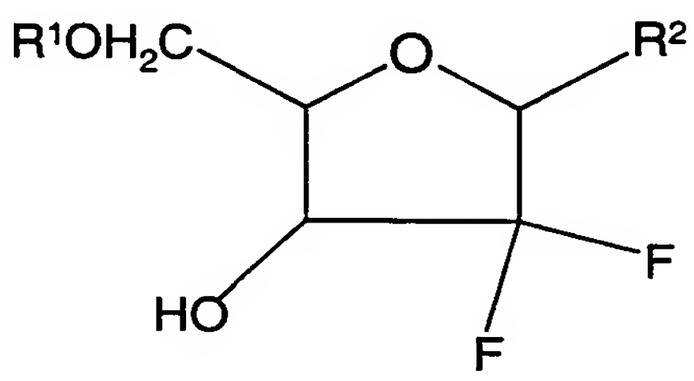
wherein:

R^6 is hydrogen or C_1-C_4 alkyl;



These compounds are disclosed in US Patent 5,464,826 which is incorporated by reference herein for its disclosure of the methods of preparing these compounds, formulating these compounds, and the treatment of cancer using these compounds.

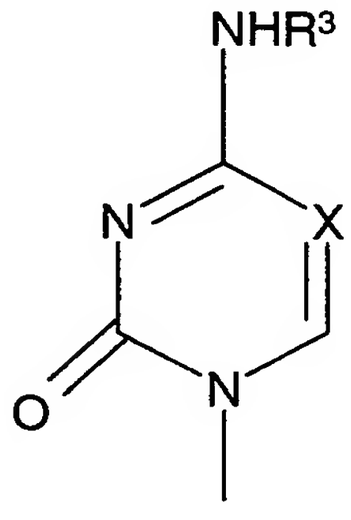
Alternatively, preferred anti-cancer compounds are described by formula:



where:

R^1 is hydrogen;

R^2 is a base defined by one of the formulae:



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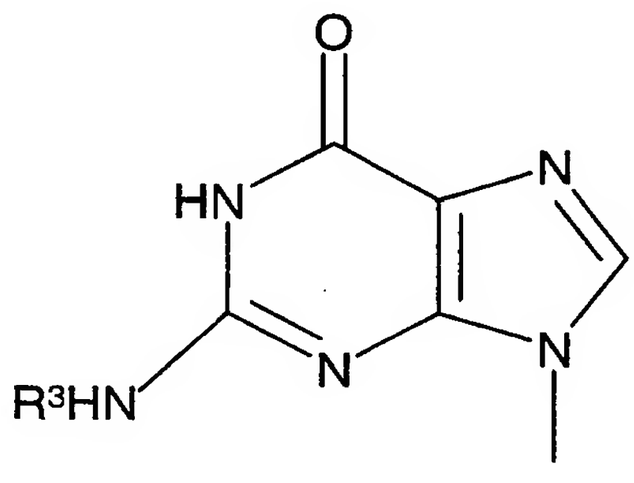

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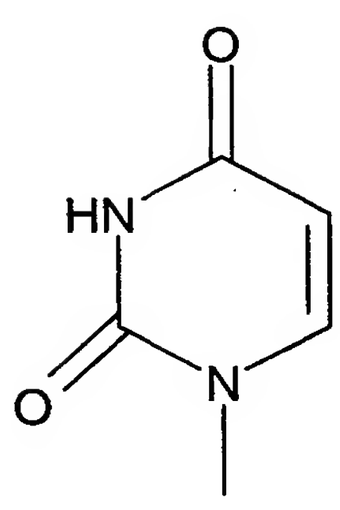
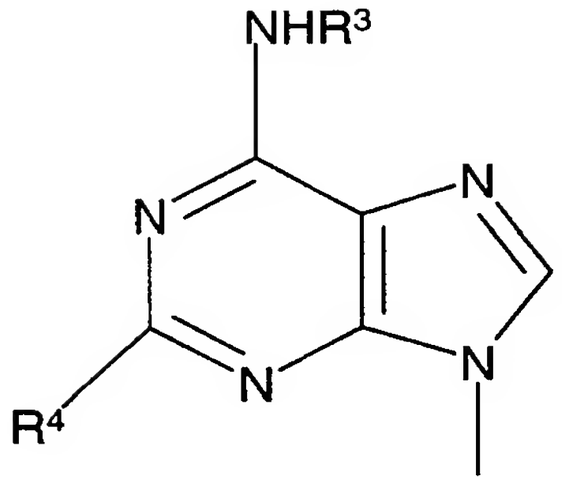



;

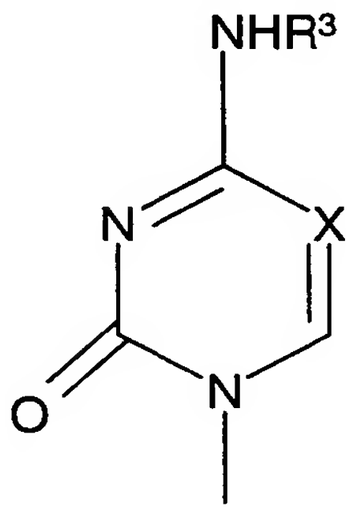
X is C-R^4;

R^3 is hydrogen;

R^4 is hydrogen, C_1-C_4 alkyl, bromo, fluoro, chloro or iodo;

and pharmaceutically acceptable salts thereof.

More preferred anti-cancer compounds are those wherein R^2 is the base defined by the formula:



.

Examples of more preferred compounds are those selected from the group consisting of the following compounds or a pharmaceutically acceptable salt thereof:

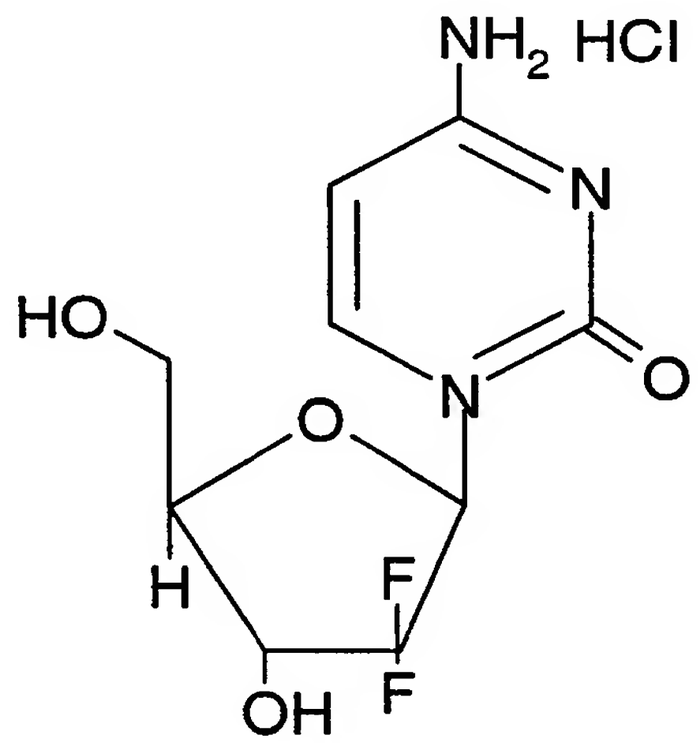
(i) 1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2',2'-difluororibose,

(ii) 1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2',2'-difluoroxylose,

(iii) 1-(2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2',2'-difluororibose, and

(iv) 1-(4-amino-5-methyl-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2',2'-difluororibose.

The most preferred compound is gemcitabine HCl which is a nucleoside analogue that exhibits antitumor activity. Gemcitabine HCl is 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer), also known as 2',2'-difluoro-2'-deoxycytidine monohydrochloride or also as 1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2',2'-difluororibose. The structural formula is as follows:



The anti-cancer agents are generally mixed with a carrier which may act as a diluent, or excipient the anti-cancer agents may be administered in the form of tablets, pills, powders lozenges, sachets, cachets, elixirs, suspensions, emulsion, solution, syrups or aerosols. Sterile injectable solutions may also be used to administer either the LTB_4 antagonist or the anti-cancer agent used in the composition or method of the invention.

The compositions of the present invention are a combination of therapeutically effective amounts of the leukotriene (LTB_4) antagonists, noted above, and a therapeutically effective amount of the anti-cancer agents noted above. The composition may be formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated elixirs or solutions for convenient oral administration or administered by intramuscular intravenous routes. The compounds can be administered transdermally and maybe formulated as sustained relief dosage forms and the like.

In another embodiment, the invention relates to a method of treating a patient suffering from a non-multi drug resistant cancerous condition which comprises the separate administration of a therapeutically effective amount of the leukotriene (LTB_4) antagonists, and the anti-cancer agent. When administered separately, the leukotriene (LTB_4) antagonists, and the anti-cancer agent may be administered on a different schedule. One may be administered before the other as long as the time between the two administrations falls within a therapeutically effective interval. Therapeutically effective interval is a period of time beginning when one of either (a) the leukotriene (LTB_4) antagonists antagonist or (b) the anti-cancer agent is administered to a human and ending at the limit of the beneficial effect in the treatment of

cancer of the combination of (a) and (b). The methods of administration of the leukotriene LTB_4 antagonist and the anti-cancer agent may vary. Thus, one agent may be administered orally, while the other is administered intravenously. It is possible that one of the products may be administered as a continuous infusion while the other is provided in discreet dosage forms. It is particularly important that the anti-cancer drug be given in the manner known to optimize its performance.

Leukotriene B_4 inhibitors suitable for (i) pharmaceutical compositions of the invention, and (ii) practicing the cancer treatment and prevention methods of the invention are as follows: calcitriol, ontazolast, Bayer Bay-x-1005, Ciba-Geigy CGS-25019C, ebselen, LeoDenmark ETH-615, Ono ONO-4057, Terumo TMK-688, Boehringer Ingleheim BI-RM-270, Ono ONO LB457, Pfizer 105696, Purdue Frederick PF 10042, Rhone-Poulenc Rorer RP 66153, SmithKline Beecham SB-201146, SmithKline Beecham SB-201993, SmithKline Beecham SB-209247, Searle SC-53228, Sumitomo SM 15178, American Home Products WAY 121006, Bayer Bay-o-8276, Warner Lambert CI-987, Warner Lambert CI-987BPC-15, MacroNex MNX-160, Merck and Co. MK-591, Merck and Co. MK-886, Ono ONO-LB-448, Purdue Frederick PF-5901, Roche Ro 25-3562, Rhone-Poulenc Rorer RG 14893, Rhone-Poulenc Rorer RP66364, Rhone-Poulenc Rorer RP69698, Shionogi S-2474, Searle SC-50605, Searle SC-41930, Searle SC-50505, Searle SC-51146, Searle SC-52798, SmithKline Beecham SK&F-104493, Leo Denmark SR-2566, Tanabe T-757, and Teijin TEI-1338, Lilly LY213024, Lilly LY264086, Lilly LY255283, Lilly LY210073, Lilly LY247833, and Lilly LY282201, 2-[3-[3-(4-acetyl-2-ethyl-5 hydroxyphenoxy)propoxy]-2-propylphenoxy]benzoic acid (US Pat. No. 5,552,441).

The LTB_4 inhibitors described above (and additional LTB_4 inhibitors) are further identified by the chemical names and sources set out below (compounds (a.) thru (vv.)) below.

Leukotriene B_4 inhibitors (and pharmaceutically acceptable salts thereof) suitable for (i) pharmaceutical compositions of the invention, and (ii) practicing the cancer treatment and prevention methods of the invention are as follows:

a) 2-[3-[3-(4-acetyl-2-ethyl-5-hydroxyphenoxy)propoxy]-2-propylphenoxy]benzoic acid (US Pat. No. 5,552,441)

b) Roche Ro 21-5535(calcitriol;(1α,3β,5Z,7E)-9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol; 1,25-Dihydroxycholecalciferol; 1,25-Dihydroxyvitamin D; 1,25-Dihydrovitamin D3; 1α,25-Dihydroxycholecalciferol; 1α,25-Dihydroxyvitamin D3; calcijex; Rocaltrol; soltriol; topitriol; CAS Registry Number 32222-06-3)

c) Parke-Davis CI-987 (5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione; CAS Registry Number 127378-46-5)

d) Pfizer CP-195543 (2-[(3S,4R)-3,4-dihyro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7-yl]-4-(trifluromethyl) benzoic acid; CAS Registry Number 204981-48-6)

e) Wyeth-Ayerst WAY-121006 (2-fluoro-4'-(2-quinolinylmethoxy)-[1,2'-biphenyl]-4-acetic acid; CAS Registry Number 136326-31-3)

f) Bayer Bay-x-1005 ((R)- α-cyclopentyl-4-(2-quinolinylmethoxy) benzeneacetic acid; CAS Registry Number 128253-31-6)

g) Ciba-Geigy CGS-25019C (4-[[5-[4-(aminoiminomethyl)phenoxy]pentyl]oxy]-3-methoxy-N,N-bis(1-methylethyl) benzamide; moxilubant; CAS Registry Number 147398-01-4)

h) Natterman & Cie GmbH ebselen (3 2-phenyl-1, 2-benzisoselenazol-3(2H)-one; CAS Registry Number 60940-34)

i) Leo Denmark ETH-615 (4-[[[(3-fluorophenyl)methyl][4-(2-quinolinylmethoxy)phenyl]amino]methyl] benzoic acid; CAS Registry Number 133430-69-0)

j) Ono ONO-4057 (2-(4-carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy] benzenepropanoic acid; CAS Registry Number 134578-96-4)

k) Terumo TMK-688 4-[5-[[2-[4-(diphenylmethoxy)-1-piperidinyl]ethyl]amino]-5-oxo-1,3-pentadienyl]-2-methoxyphenyl ethyl ester carbonic acid; CAS Registry Number 110501-66-1)

l) Boehringer Ingleheim BIRM-270 ((S)-N-[2-cyclohexyl-1-(2-pyrindyl)ethyl]-5-methyl-2-benzoxazolamine; ontazolast; CAS Registry Number 147432-77-7)

m) Ono ONO-LB457 (ONO 4057; (E)-2-(4-carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy] benzenepropanoic acid; CAS Registry Number 134578-96-4)

n) Pfizer 105696 (1-[(3S,4R)-3-([1,1'-biphenyl]-4-ylmethy)-3,4-dihydro-4-hydroxy-2H-1-benzopyran-7-yl]-cyclopentanecarboxylic acid; CAS Registry Number 158081-99-3)

o) Purdue Frederick PF 10042 (1,[5-hydroxy-5-[8-(1-hydroxy-2-phenylethyl)-2-dibenzofuranyl]-1-oxopentyl]pyrroline; CAS Registry Number 135893-33-3)

p) Rhone-Poulenc Rorer RP 66153 (α,α-dimethyl-3-(3-phenylpropyl)-2-thiopheneheptanoic acid; CAS Registry Number 142422-795)

q) SmithKline Beecham SB-201146 ((E)-3-[6-[[(3-aminophenyl)sulfinyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]-2-propenoic acid; CAS Registry Number 180208-37-1)

r) SmithKline Beecham SB-201993 ((E)-3-[[[[6-(2-carboxyethenyl)-5-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]methyl]thio]methyl] benzoic acid; CAS Registry Number 150399-22-7)

s) SmithKline Beecham SB-209247 ((E)-3-[6-[[2,6-dichlorophenyl)thio]methyl]-3-(2-phenylethoxy-2-pyridinyl]-2-propenoic acid; ticolubant; CAS Registry Number 154413-61-3)

t) Searle SC-53228 (7-[3-(2-cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy)propoxy]-3,4-dihydro-8-propyl-(S)-2H-1-benzopyran-2-propanoic acid; CAS Registry Number 153633-01-3)

u) Sumitomo SM 15178 (1-[4,11-dihydroxy-13-(4-methoxyphenyl)-1-oxo-5,7,9-tridecatrienyl] pyrrolidine; CAS Registry Number 104227-11-4)

v) Bayer Bay 0-8276 (4-chloro-N-1H-1,2,4-triazol-3-yl-benzenesulfenamide; BAY 08276 CAS Registry Number 85259-71-8)

w) Warner Lambert CI-987 (5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione; CAS Registry Number 127378-46-5)

x) Warner Lambert BPC-15 (CAS Registry Number 195215-25-9)

y) MacroNex MNX-160 (CAS Registry Number 195215-47-5)

z) Merck and Co. MK-886 (1-[(4-chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]-α,α-dimethyl-5-(1-methyethyl)-1H-indole-2-propanoic acid; L 663536; CAS Registry Number 118414-82-7)

aa) Ono ONO-LB-448(CAS Registry Number 186912-85-6)

bb) Purdue Frederick PF-5901 (α-pentyl-3-(2-quinolinylmethoxy)benzenemethanol; CAS Registry Number 101910-24-1)

cc) Roche Ro 25-3562 (3-[5-(4-chlorophenoxy)-3-methyl-3-pentenyl]-2-ethyl-2-methyl oxirane; AI 3-70356;

Roller's synthetic juvenile hormone; CAS Registry Number 38896-81-0)

dd) Rhone-Poulenc Rorer RG 14893 (4-[2-[methyl(2-phenylethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic acid; CAS Registry Number 141835-49-6)

ee) Rhone-Poulenc Rorer RP66364 (CAS Registry Number 186912-92-5)

ff) Rhone-Poulenc Rorer RP69698 (2-[[5-methyl-5-(1H-tetrazol-5-yl)hexyl]oxy]-4,6-diphenyl pyridine; CAS Registry Number 141748-00-7)

gg) Shionogi S-2474 (CAS Registry Number 195215-53-3)

hh) Searle SC-50605 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazoly)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry Number 138828-39-4)

ii) Searle SC-41930 (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry Number 120072-59-5)

jj) Searle SC-50505 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry 138828-39-4)

kk) Searle SC-51146 (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-propanoic acid; CAS Registry Number 141059-52-1)

11) Searle SC-52798 (7-[3-[4-(aminocarbonyl)-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid; CAS Registry Number 152246-97-4)

mm) SmithKline Beecham SK&F-104493 (6,7-dihydro-2-(4-methoxyphenyl)-3-(4-pyridinyl)-5H-pyrrolo[1,2-a]imidazole; CAS Registry Number 111908-95-3)

nn) Leo Denmark SR-2566 (CAS Registry Number 195215-55-5)

oo) Tanabe T-757 (CAS Registry 187112-56-7)

pp) Teijin TEI-1338 [1R-[1α,2β(E)]]-(2-[[4-[2-[2-(2-naphthalenyl)ethenyl]cyclopropyl]-1-oxobutyl]amino] benzoic acid methyl ester; CAS Registry Number 119261-58-4)

qq) Lilly LY213024 (5-(3-carboxybenzoyl)-2-)decyloxy) benzenepropanoic acid; CAS Registry Number 117423-95-7)

rr) Lilly LY264086 (7-carboxy-3-(decyloxy)-9-oxo-9H-xanthene-4-propanoic acid; CAS Registry Number 135199-82-5)

ss) Lilly LY255283 (1-[5-ethyl-2-hydroxy-4-[[6-methyl-6-(1H-tetrazol-5-yl)heptyl]oxy]phenyl] ethanone; CGS 23356; CAS Registry Number 117690-79-6)

tt) Lilly LY247833 (2-ethyoxy-4-ethyl-5-[[6-methyl-6-(2H-tetrazol-5-yl)heptyl]oxy]phenol)

uu) Lilly LY282201 (3,4-dihydro-8-propyl-7-[[3-(2-ethyl-5-hydroxy-4-ethoxyphenoxy)propyl]oxy]-2H-1-benzopyran-2-carboxylic acid),

vv) Lilly LY210073 (CAS Registry Number 186912-79-8);

and pharmaceutically acceptable acids, salts, solvates, and ester prodrugs thereof.

The above LTB_4 inhibitors are identified by company identifiers and code numbers which are readily converted to names of specific chemical compounds by using well-known databases of chemical literature and medicinal chemistry such as; "Chemical Abstracts Database" (product of Chemical Abstracts Co.) and "The Investigational Drug Database" (product of Current Drugs Ltd.).

In many cases the above specific LTB_4 inhibitors (identified by company identifiers and code numbers) are described as species in patents of the above identified companies. These patents most often describe a genus of compounds having utility as LTB_4 inhibitors, where the above identified species are single compounds within the genus taught or claimed by these patents. Therefore, all the compounds within such taught or claimed patent genera are also considered to be within the scope of the compounds considered useful in the compositions and methods of use of this invention.

A particularly preferred LTB_4 receptor antagonist for use in the compositions and method of treatment of the invention is 2-[(3S,4R)-3,4-dihydro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7-yl]-4-(trifluoromethyl) benzoic acid or a pharmaceutically acceptable salt thereof.

The salt derivatives of the LTB_4 antagonists and anti-cancer agents used in the composition and method of the invention are pharmaceutically acceptable salts, that include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium, magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid (e.g., carboxylic acid, sulfonic acid, phosphonic acid) in solution with a base or by exposing the acid to an acidic cation charged ion exchange resin. For example, a carboxylic acidic group (a preferred acidic group) may form a salt by reaction with appropriate bases (e.g., NaOH, KOH) or sodium or potassium charged acidic ion-exchange resins to yield the corresponding sodium and potassium salt.

Certain compounds of the compositions or methods of the invention may possess one or more chiral centers and

may thus exist in optically active forms. Likewise, when the compounds contain an alkenyl or alkenylene group there exists the possibility of cis- and trans- isomeric forms of the compounds. The R- and S- isomers and mixtures thereof, including racemic mixtures as well as mixtures of cis- and trans- isomers, are contemplated by this invention. Additional asymmetric carbon atoms can be present in a substituent group such as an alkyl group. All such isomers as well as the mixtures thereof are intended to be included in the invention. If a particular stereoisomer is desired, it can be prepared by methods well known in the art by using stereospecific reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively by methods which lead to mixtures of the stereoisomers and subsequent resolution by known methods. For example, a racemic mixture may be reacted with a single enantiomer of some other compound. This changes the racemic form into a mixture of diastereomers and diastereomers, because they have different melting points, different boiling points, and different solubilities can be separated by conventional means, such as crystallization.

Prodrugs are derivatives of the compounds of the invention which have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid

derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds used in the composition and method of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. Particularly preferred esters as prodrugs are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, morpholinoethyl, and N,N-diethylglycolamido.

N,N-diethylglycolamido ester prodrugs may be prepared by reaction of the sodium salt of a compound used in the composition or method of the invention (in a medium such as dimethylformamide) with 2-chloro-N,N-diethylacetamide (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA; Item No. 25,099-6).

Morpholinylethyl ester prodrugs may be prepared by reaction of the sodium salt of a compound used in the composition or method of the invention (in a medium such as dimethylformamide) 4-(2-chloroethyl)morpholine hydrochloride (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA, Item No. C4,220-3).

In one embodiment the compositions of the present invention are a combination of therapeutically effective amounts of the leukotriene (LTB_4) inhibitors, noted above and a therapeutically effective amount of an anti-cancer agent. The composition may be formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated elixirs or solutions for convenient oral administration or administered by intramuscular intravenous routes. The compounds can be

administered transdermally and maybe formulated as sustained relief dosage forms and the like.

In another embodiment, the anti-cancer agents are formulated independently of the leukotrienes (LTB_4) inhibitors and are administered separately, in any order. The anti-cancer agents may be formulated with common excipients, diluents or carriers and administered by intravenous infusion. On the other hand, the anti-cancer agents may be formulated into liquids suitable for oral administration. Anti-cancer agents may also be compressed into tablets and administered orally. If the anti-cancer agents and the leukotrienes (LTB_4) antagonists are administered separately, the anti-cancer agents may be administered before, after or during the administration of the leukotriene (LTB_4) antagonists. If the anti-cancer agents are administered separately from the leukotrienes (LTB_4) antagonists, they must be administered within a therapeutically effective interval. Typically, the anti-cancer agents and the leukotriene (LTB_4) antagonist are administered within 24 hours of each other, more preferably with 4 hours and most preferably within 1 hour.

The method of treating a human patient according to the present invention includes both the administration of the combination of leukotriene (LTB_4) antagonists and an anti-cancer agent as well as the separate administration of the leukotriene (LTB_4) antagonists and the anti-cancer agent. When administered separately, the leukotriene (LTB_4) antagonists are formulated into formulations which may be administered by the oral and rectal routes, topically, parenterally, e.g., by injection and by continuous or discontinuous intra-arterial infusion, in the form of, for example, tablets, lozenges, sublingual tablets, sachets, cachets, elixirs, gels, suspensions,

aerosols, ointments, for example, containing from 1 to 10% by weight of the active compound in a suitable base, soft and hard gelatin capsules, suppositories, injectable solutions and suspensions in physiologically acceptable media, and sterile packaged powders adsorbed onto a support material for making injectable solutions.

Ratio and Amount of Ingredients in the Composition of the Invention:

The essential ingredients (a) an LTB_4 antagonist and (b) anti-cancer compound are present in the formulation in such proportion that a dose of the formulation provides a pharmaceutically effective amount of each ingredient to the patient being treated. Typically, the weight ratio of LTB_4 antagonist to anti-cancer agent 1:100 to 100:1, preferable from 10:1 to 1:10 and most preferable from 1:4 to 4:1.

Advantageously for this purpose, compositions may be provided in dosage unit form, preferably each dosage unit containing from about 5 to about 500 mg (from about 5 to 50 mg in the case of parenteral or inhalation administration, and from about 25 to 500 mg in the case of oral or rectal administration) of a compound of Formula I or Formula II. Dosages from about 0.5 to about 300 mg/kg per day, preferably 0.5 to 20 mg/kg, of active ingredient may be administered although it will, of course, readily be understood that the amount of the compound or compounds of Formula I actually to be administered will be determined by a physician, in the light of all the relevant circumstances including the condition to be treated, the choice of compound to be administered and the choice of route of administration and therefore the above preferred dosage range is not intended to limit the scope of the present invention in any way.

The formulations useful for separate administration typically consist of the leukotriene (LTB_4) mixed with a carrier, or diluted by a carrier, or enclosed or encapsulated by an ingestible carrier in the form of a capsule, sachet, cachet, paper or other container or by a disposable container such as an ampoule. A carrier or diluent may be a solid, semi-solid or liquid material which serves as a vehicle, excipient or medium for the active therapeutic substance. Some examples of the diluents or carrier which may be employed in the pharmaceutical compositions of the present invention are lactose, dextrose, sucrose, sorbitol, mannitol, propylene glycol, liquid paraffin, white soft paraffin, kaolin, fumed silicon dioxide, microcrystalline cellulose, calcium silicate, silica, polyvinylpyrrolidone, cetostearyl alcohol, starch, modified starches, gum acacia, calcium phosphate, cocoa butter, ethoxylated esters, oil of theobroma, arachis oil, alginates, tragacanth, gelatin, syrup, methyl cellulose, polyoxyethylene sorbitan monolaurate, ethyl lactate, methyl and propyl hydroxybenzoate, sorbitan trioleate, sorbitan sesquioleate and oleyl alcohol and propellants such as trichloromonofluoromethane, dichlorodifluoromethane and dichlorotetrafluoroethane. In the case of tablets, a lubricant may be incorporated to prevent sticking and binding of the powdered ingredients in the dies and on the punch of the tableting machine. For such purpose there may be employed for instance aluminum, magnesium or calcium stearates, talc or mineral oil.

Preferred pharmaceutical forms of the present invention are capsules, tablets, suppositories, injectable solutions, creams and ointments. Especially

preferred are formulations for inhalation application, such as an aerosol, and for oral ingestion.

Pharmaceutical Compositions of the Invention

The pharmaceutical composition of the invention comprises as essential ingredients:

(a) an LTB_4 antagonist, and

(b) an anti-cancer agent.

When the pharmaceutical composition of the invention is prepared in injectable form it is a composition comprising as ingredients:

(a) an LTB_4 antagonist,

(b) an anti-cancer agent, and

(c) an injectable liquid carrier.

Pharmaceutically acceptable carriers are those well known in the medical arts, such as sterile water, sterile water containing saline, and sterile water containing sugars and/or saline.

The following formulation examples may employ as active compounds any of the leukotriene (LTB_4) antagonists noted above. The examples are illustrative only and are not intended to limit the scope of the invention in any way.

FORMULATION EXAMPLE 1

An intravenous formulation is prepared as follows:

LTB_4 antagonist, (CP-195543)	10 mg
gemcitabine hydrochloride	90 mg
isotonic saline	500 ml

The solution of the above ingredients is administered intravenously at a rate of 1 ml/minute to a mammal in need of treatment for cancer.

FORMULATION EXAMPLE 2

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
LTB_4 antagonist, (CP-195543)	25
gemcitabine hydrochloride	225
Starch	200
Magnesium stearate	10

The above ingredients are mixed and filled into hard gelatin capsules in 710mg quantities.

FORMULATION EXAMPLE 3

A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
LTB_4 antagonist, (CP-195543)	25
gemcitabine hydrochloride	225
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Magnesium stearate	5

The components are blended and compressed to form tablets each weighing 915mg.

FORMULATION EXAMPLE 4

An aerosol solution is prepared containing the following components:

	Weight %
LTB_4 antagonist, (CP-195543)	.05
gemcitabine hydrochloride	.45
Ethanol	30.00
Propellant 11 (trichlorofluoromethane)	10.00
Propellant 12 (Dichlorodifluoromethane)	29.75
Propellant 114 (Dichlorotetrafluoroethane)	29.75

The active compounds are dissolved in the ethanol and the solution is added to the propellant 11, cooled to -30°C. and transferred to a filling device. The required amount is then fed to a container and further filled with the pre-mixed propellants 12 and 114 by means of the cold-filled method or pressure-filled method. The valve units are then fitted to the container.

FORMULATION EXAMPLE 5

Tablets each containing 60 mg of active ingredient are made up as follows:

LTB_4 antagonist, (CP-195543)	12 mg
gemcitabine hydrochloride	110 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	212 mg

The active ingredients, starch and cellulose are passed through a No. 45 mesh U.S. sieve (355 μm) and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve (1.4 mm). The granules so produced are dried at 50-60° and passed through a No. 18 mesh U.S. sieve (1.00 mm). The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve (250 μm), are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 210 mg.

FORMULATION EXAMPLE 6

Capsules each containing 80 mg of medicament are made as follows:

LTB_4 antagonist, (CP-195543)	12 mg
gemcitabine hydrochloride	110 mg
Starch	60 mg
Microcrystalline cellulose	60 mg
Magnesium stearate	2 mg
Total	244 mg

The active ingredients, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve (355 μm), and filled into hard gelatin capsules in 244 mg quantities.

FORMULATION EXAMPLE 7

Suppositories each containing 250 mg of active ingredients are made as follows:

LTB_4 antagonist, (CP-195543)	25 mg
gemcitabine hydrochloride	225 mg
Unsaturated or saturated fatty acid glycerides to	2,000 mg

The active ingredients are passed through a No. 60 mesh U.S. sieve (250 μm) and suspended in the fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

FORMULATION EXAMPLE 8

Suspensions each containing 50 mg of medicament per 5 mL dose are made as follows:

LTB_4 antagonist, (CP-195543)	10 mg
gemcitabine hydrochloride	90 mg
Sodium carboxymethyl cellulose	50 mg
Sugar	1 g
Methyl paraben	0.05 mg
Propyl paraben	0.03 mg
Flavor	q.v.
Color	q.v.
Purified water	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve (355 μm) and mixed with the sodium carboxymethylcellulose, sugar, and a portion of the water to form a suspension. The parabens, flavor and color are dissolved and diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

The leukotriene (LTB_4) antagonists are generally administered prior, during and after the 2',2'-difluoronucleoside anti-cancer agent is administered. If the leukotriene (LTB_4) antagonists are administered after the 2',2'-difluoronucleoside anti-cancer agent they should be administered within a therapeutically effective interval.

ASSAY EXAMPLE 1

The Nude Mouse Xenograft test used to evaluate anti-oncolytic agents of this invention is well known and generally described in the textbook; Beverly A Teicher, Editor, Anticancer Drug Development Guide, Humana Press, Totowa, New Jersey, 1997, p.75-124 (ISBN 0-89603-461-5); the disclosure of which is incorporated herein by reference. The xenograft test is more particularly described as follows:

Male or female nude mice, selected as appropriate to the gender of the tumor (Charles River), were treated with total body *gamma* Radiation (450 rads). After 24 hours, human BxPC-3 pancreatic carcinoma, (available from American Type culture Collection, Manassas, VA) prepared from a brie of donor tumors (5×10^6 cells), were implanted subcutaneously in a hind-leg of the mice. The mice were treated with the LTB_4 antagonist, 2-[(3S,4R)-

3,4-dihydro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7-yl]-4-(trifluoromethyl) benzoic acid (CP-195543), at dosages of 1, 3, or 10 mg per kilogram daily, administered orally, beginning 4 days after the tumor cell implantation. Gemcitabine (60mg/kg) was administered intraperitoneally.

Tumor response was monitored by tumor volume measurement performed twice per week over the course of 60-90 days. Body weights were determined as a general measurement of toxicity. The mice were divided into an untreated control group and multiple treatment groups with five mice in each group.

The data was analyzed by determining the mean tumor volume for the control group and each treatment group over the course of the experiment. The tumor growth delay was calculated as the difference in days for the treatment versus the control tumors to reach the volume of 1000 mm^3.

Table 1

Mouse Xenograft Test Results

Growth Delay of Pancreatic Tumor(1)

Treatment	Dose CP-195543	Dose GEM	TGD	TGD, sem
CP-195543	1	-	0.6	0.3
CP-195543	3	-	2.6	0.3
CP-195543	10	-	4.5	0.4
GEM	-	60	19.2	1.8
CP-195543 + GEM	1	60	14.9	1.4
CP-195543 + GEM	3	60	26.3	2.5
CP-195543 + GEM	10	60	34.1	3.3

(1) = Human BxPC3 pancreatic carcinoma

CP-195543 = 2-[(3S,4R)-3,4-dihydro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7-yl]-4-(trifluoromethyl) benzoic acid; $C_{24}H_{19}F_3O_4$; Chemical Abstract Registry Number 204981-48-6

GEM = gemcitabine hydrochloride, a 2',2'-difluoro-2'-deoxycytidine; 2'-deoxy-2',2'-difluorocytidine; molecular formula $C_9H_{11}F_2N_3O_4$; Chemical Abstract Registry Number 95058-81-4, a product of Eli Lilly and Company

Dose = milligrams per kilogram mouse body weight

TGD = average tumor growth delay in days

sem = standard error of the mean

Detailed Description of the Drawing:

Figure 1 displays the data in Table 1, supra. The Figure illustrates the increased effectiveness of a combination treatment of (i) CP-195543 and (ii)

gemcitabine hydrochloride in delaying tumor growth over the use of the individual agents (i) or (ii).

Fig. 1 - displays various treatments for Human BxPC3 pancreatic carcinoma.
Bars (1), (2), and (3) display tumor growth delay resulting from use of CP-195543, alone at doses of 1, 3, and 10 mg/kg, respectively.

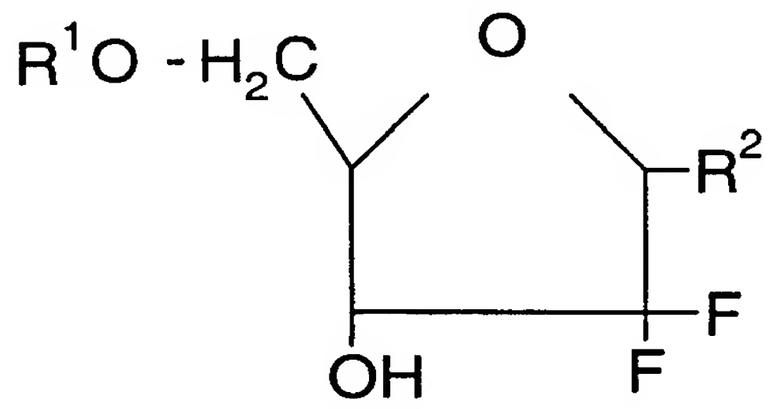
Bar (4) displays tumor growth delay for the anti-cancer agent, gemcitabine hydrochloride, alone at a dose of 60 mg/kg.

Bars (5), (6), and (7) display tumor growth delay resulting from combined use of CP-195543 (at doses of 1, 3, and 10 mg/kg) and gemcitabine hydrochloride (at a dose of 60 mg/kg); respectively.

We Claim:

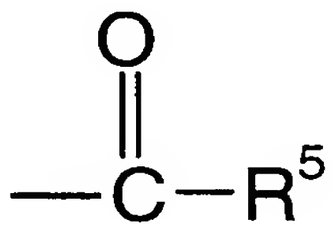
1. A composition of matter comprising a therapeutically effective amount of a leukotriene (LTB_4) antagonist and a 2',2'-difluoronucleoside anti-cancer agent.

2. The composition of claim 1 wherein the 2',2'-difluoronucleoside anti-cancer agent is represented by the formula:

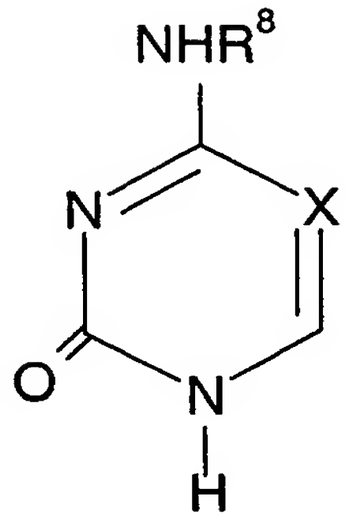


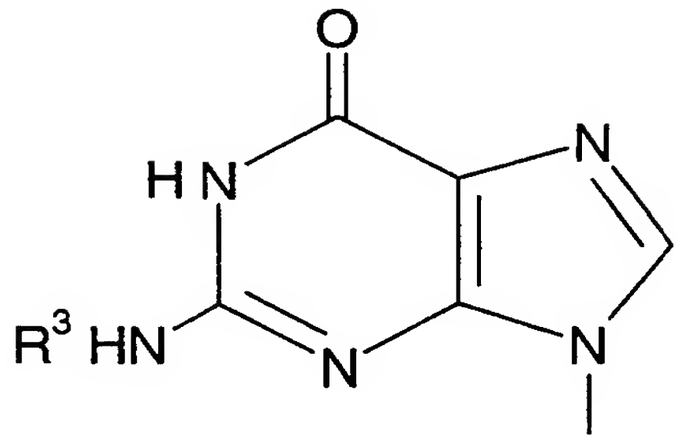
wherein:

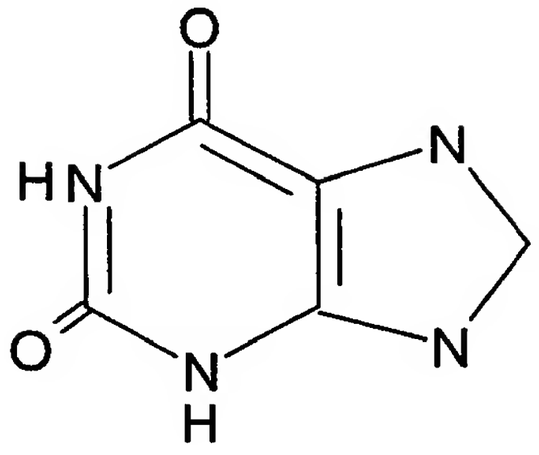
R1 is hydrogen or

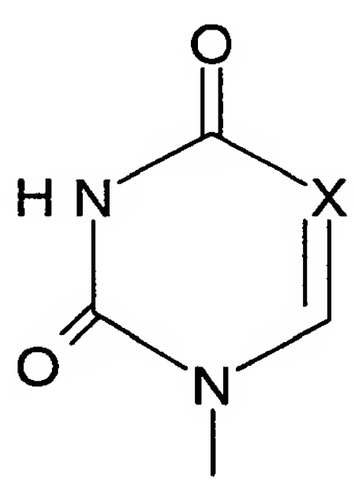


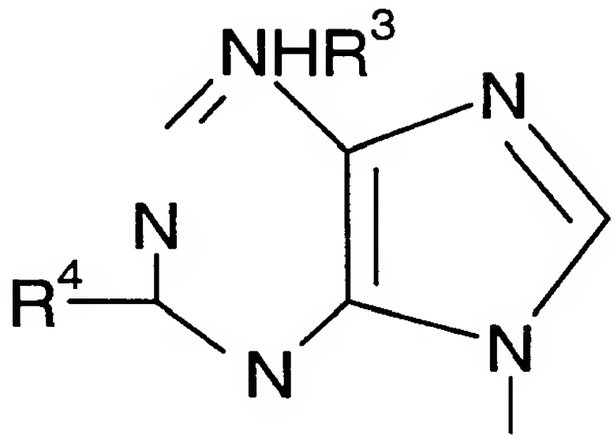
R^2 is a base defined by one of the formulae





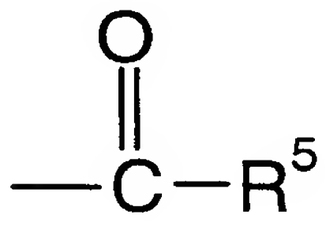






X is N or C-R^4

R^3 is hydrogen, C_1-C_4 alkyl or



R^4 is hydrogen, C_1-C_4 alkyl, amino, bromo, fluoro, chloro or iodo;

each R^5 independently is hydrogen or C_1-C_4 alkyl; or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof.

3. A composition of matter comprising a therapeutically effective amount of leukotriene (LTB_4) antagonist and a therapeutically effective amount of 2',2'-difluoronucleoside anti-cancer agent;
wherein the leukotriene (LTB_4) antagonist is selected from the group consisting of compounds (a) thru (uu) as follows:

a) 2-[3-[3-(4-acetyl-2-ethyl-5-hydroxyphenoxy)propoxy]-2-propylphenoxy]benzoic acid;

b) (1α,3β,5Z,7E)-9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol; 1,25-Dihydroxycholecalciferol; 1,25-Dihydroxyvitamin D; 1,25-Dihydrovitamin D3; 1α,25-Dihydroxycholecalciferol; 1α,25-Dihydroxyvitamin D3;

c) (5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione;

d) (2-[(3S,4R)-3,4-dihyro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7-yl]-4-(trifluromethyl) benzoic acid;

e) (2-fluoro-4'-(2-quinolinylmethoxy)-[1,2'-biphenyl]-4-acetic acid;

f) ((R)- α-cyclopentyl-4-(2-quinolinylmethoxy) benzeneacetic acid;

g) (4-[[5-[4-(aminoiminomethyl)phenoxy]pentyl]oxy]-3-methoxy-N,N-bis(1-methylethyl) benzamide;

h) (3 2-phenyl-1,2-benzisoselenazol-3(2H)-one;

i) (4-[[[(3-fluorophenyl)methyl][4-(2-quinolinylmethoxy)phenyl]amino]methyl] benzoic acid;

j) (2-(4-carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy] benzenepropanoic acid;

k) 4-[5-[[2-[4-(diphenylmethoxy)-1-piperidinyl]ethyl]amino]-5-oxo-1,3-pentadienyl]-2-methoxyphenyl ethyl ester carbonic acid;

l) ((S)-N-[2-cyclohexyl-1-(2-pyrindyl)ethyl]-5-methyl-2-benzoxazolamine; ontazolast;

m) (ONO 4057; (E)-2-(4-carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy] benzenepropanoic acid;

n) (1-[(3S,4R0-3-([1,1'-biphenyl]-4-ylmethy)-3,4-dihydro-4-hydroxy-2H-1-benzopyran-7-yl]-Cyclopentanecarboxylic acid;

o) (1,[5-hydroxy-5-[8-(1-hydroxy-2-phenylethyl)-2-dibenzofuranyl]-1-oxopentyl] pyrroline;

p) (α,α-dimethyl-3-(3-phenylpropyl)-2-thiopheneheptanoic acid;

q) ((E)-3-[6-[[(3-aminophenyl)sulfinyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]-2-propenoic acid;

r) ((E)-3-[[[[6-(2-carboxyethenyl)-5-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]methyl]thio]methyl] benzoic acid;

s) ((E)-3-[6-[[2,6-dichlorophenyl)thio]methyl]-3-(2-phenylethoxy-2-pyridinyl]-2-propenoic acid; ticolubant;

t) (7-[3-(2-cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy)propoxy]-3,4-dihydro-8-propyl-(S)-2H-1-benzopyran-2-propanoic acid;

u) (1-[4,11-dihydroxy-13-(4-methoxyphenyl)-1-oxo-5,7,9-tridecatrienyl] pyrrolidine;

v) (4-chloro-N-1H-1,2,4-triazol-3-yl-benzenesulfenamide;

w) (5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione;

x) Warner Lambert BPC-15 (CAS Registry Number 195215-25-9)

y) MacroNex MNX-160 (CAS Registry Number 195215-47-5)

z) (1-[(4-chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]-α,α-dimethyl-5-(1-methyethyl)-1H-indole-2-propanoic acid; L 663536;

aa) Ono ONO-LB-448(CAS Registry Number 186912-85-6)

bb) (α-pentyl-3-(2-quinolinylmethoxy) benzenemethanol;

cc) (3-[5-(4-chlorophenoxy)-3-methyl-3-pentenyl]-2-ethyl-2-methyl oxirane;

dd) (4-[2-[methyl(2-phenylethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic acid;

ee) Rhone-Poulenc Rorer RP66364 (CAS Registry Number 186912-92-5)

ff) (2-[[5-methyl-5-(1H-tetrazol-5-yl)hexyl]oxy]-4,6-diphenyl pyridine;

gg) Shionogi S-2474 (CAS Registry Number 195215-53-3)

hh) (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazoly)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

ii) (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

jj) (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

kk) (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-propanoic acid;

ll) (7-[3-[4-(aminocarbonyl)-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

mm) (6,7-dihydro-2-(4-methoxyphenyl)-3-(4-pyridinyl)-5H-Pyrrolo[1,2-a]imidazole;

nn) Leo Denmark SR-2566 (CAS Registry Number 195215-55-5)

oo) Tanabe T-757 (CAS Registry 187112-56-7)

pp) [1R-[1α,2β(E)]]-(2-[[4-[2-[2-(2-naphthalenyl)ethenyl]cyclopropyl]-1-oxobutyl]amino] benzoic acid methyl ester;

qq) (5-(3-carboxybenzoyl)-2-)decyloxy) benzenepropanoic acid;

rr) (7-carboxy-3-(decyloxy)-9-oxo-9H-xanthene-4-propanoic acid;

ss) (1-[5-ethyl-2-hydroxy-4-[[6-methyl-6-(1H-tetrazol-5-yl)heptyl]oxy]phenyl] ethanone; CGS 23356;

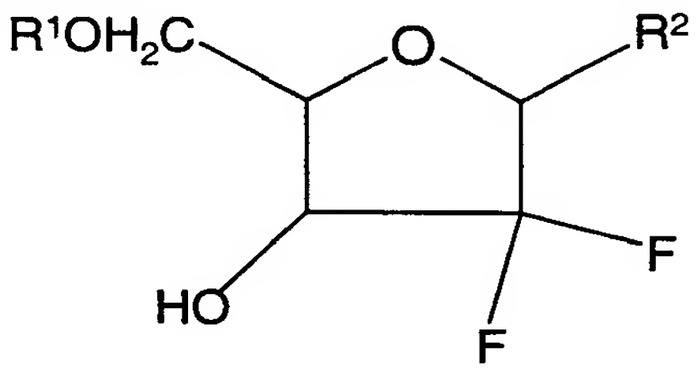
tt) (2-ethyoxy-4-ethyl-5-[[6-methyl-6-(2H-tetrazol-5-yl)heptyl]oxy]phenol); and

uu) (3,4-dihydro-8-propyl-7-[[3-(2-ethyl-5-hydroxy-4-ethoxyphenoxy)propyl]oxy]-2H-1-benzopyran-2-carboxylic acid);

vv) Lilly LY210073 (CAS Registry Number 186912-79-8);

or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof; and

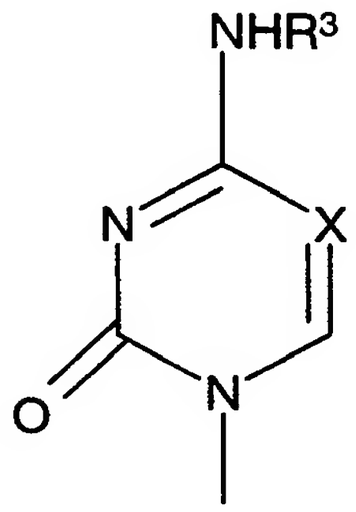
wherein the 2',2'-difluoronucleoside anti-cancer agent represented by the formula:



where:

R^1 is hydrogen;

R^2 is a base defined by one of the formulae: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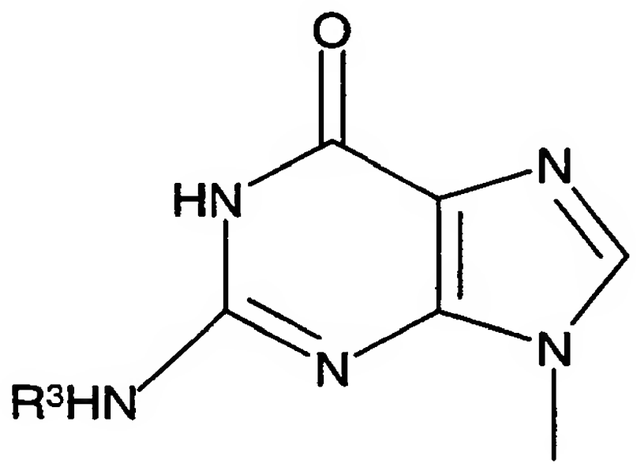
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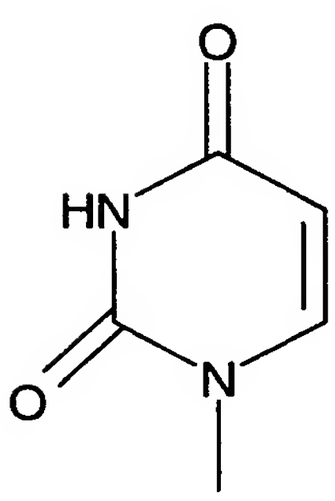
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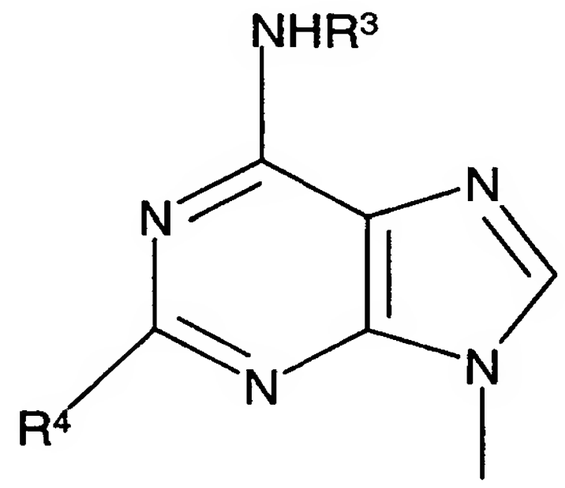

;

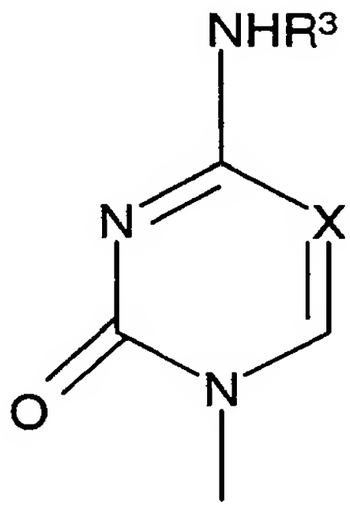
X is C-R^4;

R^3 is hydrogen;

R^4 is hydrogen, C_1-C_4 alkyl, bromo, fluoro, chloro or iodo;

and pharmaceutically acceptable salts, solvate, or prodrug derivative thereof.

4. The composition of claim 3 wherein for the anti-cancer compound R^2 is a base represented by the formula:



5. The composition of claim 1 or 3 or 4 wherein the anti-cancer agent is selected from the group consisting of the following compounds or a pharmaceutically acceptable salt thereof:

(i) 1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2',2'-difluororibose,

(ii) 1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2',2'-difluoroxylose,

(iii) 1-(2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2',2'-difluororibose, and

(iv) 1-(4-amino-5-methyl-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2',2'-difluororibose.

6. The composition according to claim 1 or 3 or 4 wherein the 2', 2'-difluornucleoside is gemcitabine HCl, namely 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer) or 1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2',2'-difluororibose.

7. The composition of claim 1 or 3 or 4 wherein the leukotriene (LTB_4) antagonist is 2-[(3S,4R)-3,4-dihydro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7-yl]-4-(trifluoromethyl) benzoic acid or a pharmaceutically acceptable salt thereof.

8. The composition of claim 7 wherein the 2',2'-difluoronucleoside anti-cancer agent is gemcitabine hydrochloride.

9. The composition of claim 1 or 3 or 4 wherein the (LTB_4) antagonist is 2-[(3S,4R)-3,4-dihydro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7-yl]-4-(trifluoromethyl) benzoic acid.

10. The composition of claim 1 or 3 or 4 wherein the weight ratio of LTB_4 antagonist to anti-cancer agent is from 1:100 to 100:1.

11. Use of the composition of matter containing leukotriene (LTB_4) antagonist and anti-cancer agent of any one of claims of claim 1 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 for the manufacture of a medicament for the treatment of cancer in mammals.

12. A method of treating cancer in a mammal by administering to said patient a composition of matter comprising a therapeutically effective amount of a leukotriene (LTB_4) antagonist and a 2',2'-difluoronucleoside anti-cancer agent.

13. A method of treating cancer in a mammal by administering to said patient composition of matter a therapeutically effective amount of leukotriene (LTB_4)

antagonist and a therapeutically effective amount of 2',2'-difluoronucleoside anti-cancer agent;

wherein the leukotriene (LTB_4) antagonist is selected from the group consisting of compounds (a) thru (uu) as follows:

a) 2-[3-[3-(4-acetyl-2-ethyl-5-hydroxyphenoxy)propoxy]-2-propylphenoxy]benzoic acid;

b) (1α,3β,5Z,7E)-9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol; 1,25-Dihydroxycholecalciferol; 1,25-Dihydroxyvitamin D; 1,25-Dihydrovitamin D3; 1α,25-Dihydroxycholecalciferol; 1α,25-Dihydroxyvitamin D3;

c) (5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione;

d) (2-[(3S,4R)-3,4-dihyro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7-yl]-4-(trifluromethyl) benzoic acid;

e) (2-fluoro-4'-(2-quinolinylmethoxy)-[1,2'-biphenyl]-4-acetic acid;

f) ((R)- α-cyclopentyl-4-(2-quinolinylmethoxy) benzeneacetic acid;

g) (4-[[5-[4-(aminoiminomethyl)phenoxy]pentyl]oxy]-3-methoxy-N,N-bis(1-methylethyl) benzamide;

h) (3 2-phenyl-1,2-benzisoselenazol-3(2H)-one;

i) (4-[[[(3-fluorophenyl)methyl][4-(2-quinolinylmethoxy)phenyl]amino]methyl] benzoic acid;

j) (2-(4-carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy] benzenepropanoic acid;

k) 4-[5-[[2-[4-(diphenylmethoxy)-1-piperidinyl]ethyl]amino]-5-oxo-1,3-pentadienyl]-2-methoxyphenyl ethyl ester carbonic acid;

l) ((S)-N-[2-cyclohexyl-1-(2-pyrindyl)ethyl]-5-methyl-2-benzoxazolamine; ontazolast;

m) (ONO 4057; (E)-2-(4-carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy] benzenepropanoic acid;

n) (1-[(3S,4R)-3-([1,1'-biphenyl]-4-ylmethy)-3,4-dihydro-4-hydroxy-2H-1-benzopyran-7-yl]-Cyclopentanecarboxylic acid;

o) (1,[5-hydroxy-5-[8-(1-hydroxy-2-phenylethyl)-2-dibenzofuranyl]-1-oxopentyl] pyrroline;

p) (α,α-dimethyl-3-(3-phenylpropyl)-2-thiopheneheptanoic acid;

q) ((E)-3-[6-[[(3-aminophenyl)sulfinyl]methyl]-3-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]-2-propenoic acid;

r) ((E)-3-[[[[6-(2-carboxyethenyl)-5-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]methyl]thio]methyl] benzoic acid;

s) ((E)-3-[6-[[2,6-dichlorophenyl)thio]methyl]-3-(2-phenylethoxy-2-pyridinyl]-2-propenoic acid; ticolubant;

t) (7-[3-(2-cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy)propoxy]-3,4-dihydro-8-propyl-(S)-2H-1-benzopyran-2-propanoic acid;

u) (1-[4,11-dihydroxy-13-(4-methoxyphenyl)-1-oxo-5,7,9-tridecatrienyl] pyrrolidine;

v) (4-chloro-N-1H-1,2,4-triazol-3-yl-benzenesulfenamide;

w) (5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-2,4-thiazolidinedione;

x) Warner Lambert BPC-15 (CAS Registry Number 195215-25-9)

y) MacroNex MNX-160 (CAS Registry Number 195215-47-5)

z) (1-[(4-chlorophenyl)methyl]-3-[(1,1-dimethylethyl)thio]-α,α-dimethyl-5-(1-methyethyl)-1H-indole-2-propanoic acid; L 663536;

aa) Ono ONO-LB-448(CAS Registry Number 186912-85-6)

bb) (α-pentyl-3-(2-quinolinylmethoxy) benzenemethanol;

cc) (3-[5-(4-chlorophenoxy)-3-methyl-3-pentenyl]-2-ethyl-2-methyl oxirane;

dd) (4-[2-[methyl(2-phenylethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic acid;

ee) Rhone-Poulenc Rorer RP66364 (CAS Registry Number 186912-92-5)

ff) (2-[[5-methyl-5-(1H-tetrazol-5-yl)hexyl]oxy]-4,6-diphenyl pyridine;

gg) Shionogi S-2474 (CAS Registry Number 195215-53-3)

hh) (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazoly)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

ii) (7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

jj) (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-(4-thiazolyl)phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

kk) (7-[3-[2-(cyclopropylmethyl)-3-methoxy-4-[(methylamino)carbonyl]phenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-propanoic acid;

11) (7-[3-[4-(aminocarbonyl)-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

mm) (6,7-dihydro-2-(4-methoxyphenyl)-3-(4-pyridinyl)-5H-Pyrrolo[1,2-a]imidazole;

nn) Leo Denmark SR-2566 (CAS Registry Number 195215-55-5)

oo) Tanabe T-757 (CAS Registry 187112-56-7)

pp) [1R-[1α,2β(E)]]-(2-[[4-[2-[2-(2-naphthalenyl)ethenyl]cyclopropyl]-1-oxobutyl]amino] benzoic acid methyl ester;

qq) (5-(3-carboxybenzoyl)-2-)decyloxy) benzenepropanoic acid;

rr) (7-carboxy-3-(decyloxy)-9-oxo-9H-xanthene-4-propanoic acid;

ss) (1-[5-ethyl-2-hydroxy-4-[[6-methyl-6-(1H-tetrazol-5-yl)heptyl]oxy]phenyl] ethanone; CGS 23356;

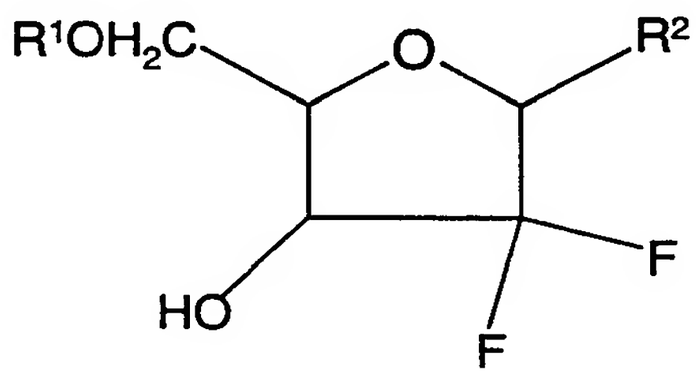
tt) (2-ethyoxy-4-ethyl-5-[[6-methyl-6-(2H-tetrazol-5-yl)heptyl]oxy]phenol); and

uu) (3,4-dihydro-8-propyl-7-[[3-(2-ethyl-5-hydroxy-4-ethoxyphenoxy)propyl]oxy]-2H-1-benzopyran-2-carboxylic acid);

vv) Lilly LY210073 (CAS Registry Number 186912-79-8);

or a pharmaceutically acceptable salt, solvate, or prodrug derivative thereof; and

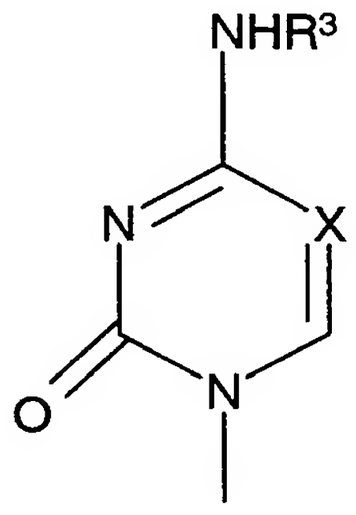
wherein the 2',2'-difluoronucleoside anti-cancer agent represented by the formula:



where:

R^1 is hydrogen;

R^2 is a base defined by one of the formulae:



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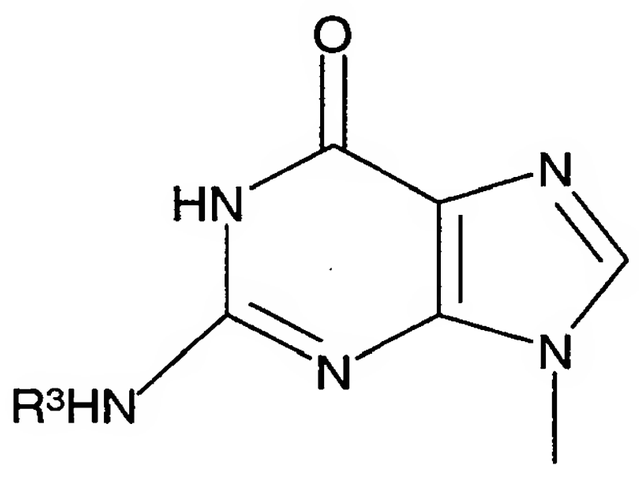

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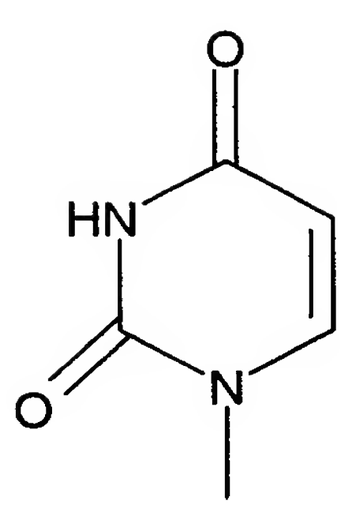
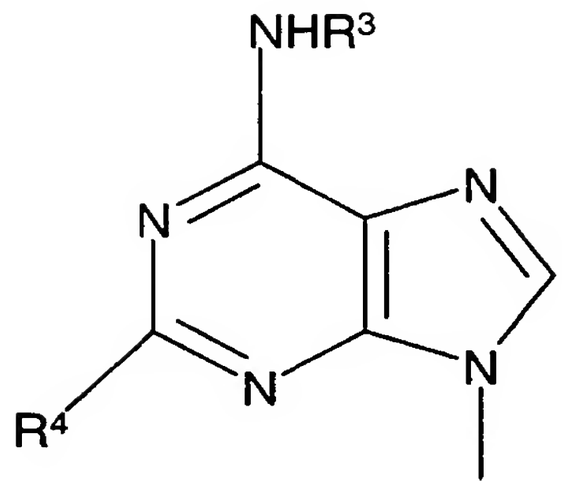



;

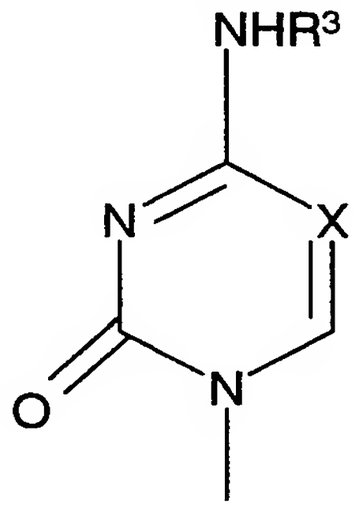
X is C-R^4;

R^3 is hydrogen;

R^4 is hydrogen, C_1-C_4 alkyl, bromo, fluoro, chloro or iodo;

and pharmaceutically acceptable salts, solvate, or prodrug derivative thereof.

14. The method of claim 13 wherein for the anti-cancer compound R^2 is a base represented by the formula:



15. The method of claim 13 wherein for the anti-cancer compound R^2 wherein the anti-cancer agent is selected from the group consisting of the following compounds or a pharmaceutically acceptable salt thereof:

(i) 1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2',2'-difluororibose,

(ii) 1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2',2'-difluoroxylose,

(iii) 1-(2,4-dioxo-1H,3H-pyrimidin-1-yl)-2-desoxy-2',2'-difluororibose, and

(iv) 1-(4-amino-5-methyl-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2',2'-difluororibose.

16. The method of claim 13 wherein the 2', 2'-difluornucleoside anti-cancer compound is selected from 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer) or 1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2',2'-difluororibose.

17. The method of claim 13 wherein the leukotriene (LTB_4) antagonist is 2-[(3S,4R)-3,4-dihydro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7-yl]-4-(trifluoromethyl) benzoic acid or a pharmaceutically acceptable salt thereof.

18. The method of claim 13 or 17 wherein the 2',2'-difluoronucleoside anti-cancer agent is gemcitabine hydrochloride.

19. The method of claim 13 wherein the (LTB_4) antagonist is 2-[(3S,4R)-3,4-dihydro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7-yl]-4-(trifluoromethyl) benzoic acid.

20. The method of claim 13 wherein the weight ratio of LTB_4 antagonist to 2',2'-difluoronucleoside anti-cancer agent is from 1:100 to 100:1.

21. The method of claim 13 wherein the from 0.5 to 300 mg/kg per day of the composition of claim 3 is administered to a mammal in need thereof.

FIG. 1